

Use of Vaccines Outside of the Cold Chain

A Literature Review

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Executive summary

This study is a compilation of the literature available on the use of vaccines out of the cold chain (OCC). Most of the studies analyzed in this review on use of vaccines OCC focus on hepatitis B (HB), with one exception—a study examining meningococcal C vaccine. Most of the studies discussed showed that there are no significant serological differences between children who receive the vaccine (HB or meningococcal C) vaccine stored outside of the cold chain and those who received the vaccine stored in the cold chain. A study on vaccine vial monitor (VVM) use during “cool” transfer using water packs rather than ice packs showed that VVMs are a valuable and useful tool for OCC practice. These data support further work to advance a policy supporting some storage and transport of HB vaccine OCC.

Introduction

Global trends in immunization coverage continue to increase, according to the World Health Organization (WHO) and the United Nations Children's Fund. However, certain areas of the world continue to struggle to meet the immunization requirements for their populations. This is the case in particular with certain vaccines, such as HB. The global coverage for this vaccine is estimated at only 60%, and regions with high rates of infection as the South East Asian Region have coverage of only 28%, while Africa has 49% and the Americas 89%.¹

In lower-income countries, the efforts to meet immunization targets are often hampered by poor health delivery systems, low political commitment, low levels of investment, poorly maintained cold chains, lack of human resources, and effective disease surveillance and reporting systems among other issues. One of the main constraints for lower-income countries to achieve immunization targets is maintaining a cold chain. Based on several studies, explained in more detail in this paper, the introduction of an out-of-the-cold-chain (OCC) strategy for heat stable vaccines has the potential for increasing immunization coverage by allowing short term transport of these vaccines OCC. In addition, this strategy may avoid problems with freezing, noted to be one of the primary cold chain problems threatening vaccine integrity.^{2,3} VVMs can be an important tool for monitoring heat exposure when vaccines are taken OCC.

This literature review summarizes published information about the experience of countries or programs that have practiced delivery of vaccines OCC, and the performance of VVMs in the field.

Literature search strategy

Various publications available on OCC use of vaccines and use of VVMs were sought using PubMed and ISI Web of Knowledge (includes science citation index expanded, social sciences citation index, arts and humanities citation index, and Medline). The keywords for the search were Vaccin, "cold chain" AND vaccin*, drug storage AND vaccin*, refrigeration AND vaccin*, "vaccine vial monitor*", thermostab* (thermostable, thermostability, thermostabilization), thermostab* AND vaccin*. Information was also sought after through email and phone conversations with internationally recognized experts in the field. For information regarding vaccine policy and current use of vaccines OCC, we referred to WHO publications including the Weekly Epidemiological Record.

Review of the literature

Use of vaccines out of cold chain

Study 1: Hepatitis B (HB) vaccine delivery outside the cold chain: the Long-An county, China example. Global Perspectives on Hepatitis. International Task Force on Hepatitis B Immunization, PATH. 1991;2:3-4.

This study was performed in Long-An County, China and sponsored by China's Expanded Programme for Immunization (EPI). The study included a research component designed to explore mechanisms for integrating HB vaccine into the immunization schedule. In Long-An County, the majority of births (80.5%) occur at home and are attended by village midwives or

village doctors. In the program, vaccine administered by village midwives was delivered to the home of each midwife on a quarterly basis for storage at room temperature. The plasma-derived HB vaccine administered by the village doctors was maintained in cold storage until given to the infant within 72 hours after birth. The village doctors were notified of the births by the village midwives within 12 hours of delivery. The second and third doses of HB were given with other EPI vaccines as part of mobile outreach services.⁴

A sero-survey was performed to examine the seroconversion rate of HB antibody in babies who received a birth-dose vaccine stored at room temperature versus under refrigeration. The survey was performed after the infants had received the three doses of HB vaccine. The study group included 590 infants aged 10 to 20 months. Of the study group, 358 infants received their birth dose from vaccine stored at ambient temperatures and administered by a village midwife, and 232 infants received vaccine stored in refrigerators and administered by a village doctor. The seroconversion rate was 81.6% in the OCC group and 81.9% in the refrigeration group. Maternal HB surface antigen (HBsAg) rates were 15.4% and 20.7% respectively. There was no difference between HBsAg rates amongst vaccinated infants in the OCC and refrigeration groups (1.1% vs. 2.2%). All HBsAg positive infants were born to HBsAg positive mothers. The estimated protective efficacy of vaccination (the percent reduction in HBsAg attributable to vaccination amongst infants exposed to HB virus) was similar at 84.5% and 77.8%, respectively in the two groups.^{4,5} Preliminary findings in this study demonstrated that HB vaccine stored OCC for up to three months can remain effective and be delivered to infants at birth.

Study 2: Home delivery of heat-stable vaccines in Indonesia: outreach immunization with a prefilled, single-use injection device. Sutanto A, Suarnawa IM, Nelson CM, Stewart T, Soewarso I. Bulletin of the World Health Organization. 1999; 77(2):119-126.

A study conducted from July 1995 to April 1996 in the Indonesian Islands of Lombok and Bali involved 110 midwives in the delivery of HB vaccine to infants and tetanus toxoid to their mothers.⁶ During the study, instead of standard disposable syringes with multidose vials, village midwives used the Uniject[®] device a prefilled, single-dose, autodisable injection device. Provincial and district supervisors trained the midwives prior to the study. All Uniject injections were given at the homes of newborn infants. Questionnaires and interviews were used to gather data from mothers and midwives.

The plasma-derived HB was distributed from the Indonesian vaccine manufacturer Perum Bio Farma, and was kept under normal cold-chain conditions during transport and storage at the health centers. After the midwives had picked up supplies of vaccine-filled Uniject devices at the health centers, they were allowed to keep them under ambient conditions for up to one month.

A potency test and a serological analysis were conducted during the study to ensure safety and efficiency of the storage strategy. Training and a threshold heat indicator were also used to prevent heat exposure. The threshold heat indicator was attached to each box to determine if the vaccines were exposed to damaging temperatures. The heat indicator changed color when exposed to temperatures $\geq 49^{\circ}\text{C}$.

Infants received the birth dose of HB vaccine delivered either with a standard syringe and vaccine stored in the cold chain, or with the Uniject device prefilled with vaccine stored for one month OCC. Seroconversion rates were identical for the two groups.

Study 3: Hepatitis B vaccination of newborn infants in rural China: Evaluation of a village-based, out of cold chain delivery strategy. Wang L, Chen H, Li F, Armstrong G, Nelson C, Ze W, Shapiro C. Bulletin of the World Health Organization. 2007; 85(9):649–732.

Another study funded by PATH using HB vaccine OCC for vaccination of newborn infants in rural China involved two groups of newborns. Group 1 used HB vaccine packaged in single-dose ampoules, stored within the cold chain, and administered to 401 infants in township hospitals. Group 2 used HB vaccine packaged in single-dose ampoules but stored OCC in villages and administered by village health workers to 391 infants in their homes. Group 3 used the same strategy as group 2 but with HB vaccine packaged in Uniject administered to 410 infants. Training of immunization providers and communication to the public regarding the importance of the birth dose were done for all three groups.⁷

Two surveys were conducted, one before study implementation (baseline-coverage survey) and one after (follow-up coverage survey), to evaluate the impact of the interventions on the on-time administration of the HB vaccine birth dose. From each of the study groups, 40 villages (clusters) were chosen at random with probability proportional to size.

In a separate survey (serological survey) to compare antibody responses to the vaccine, approximately 200 children from each group were selected at random at the end of the study to participate in a seroconversion evaluation. Eligibility was restricted to children aged 7 to 11 months old who had received all three doses of the HB vaccine including a birth dose (defined as a dose within 24 hours of birth) and who had received the last dose at least a month before the survey. All serum specimens were tested for HBsAg, antibody to HBsAg (anti-HBs), and antibody to HB core antigen (anti-HBc). While the baseline three-dose HB vaccine coverage was over 70% in all three study groups, the baseline birth-dose vaccine coverage was only 8.7%. Birth-dose vaccine coverage increased in all three groups by the end of the study to 57.9% among group-1 children (ampoule inside the cold chain), 67.8% among group-2 children (ampoule outside the cold chain), and 77.3% among group-3 children (HB Uniject outside the cold chain). Birth-dose coverage was not statistically significantly different between study groups at baseline but higher in group 3 than in group 1 on follow up.

Of the 606 children in the serologic survey who received three HB vaccine doses, one of which was at birth, 580 (96%) had detectable anti-HBs levels and 89% had levels ≥ 10 U/ml, considered protective. There were no significant differences between groups in the proportion of infants with sero-protective levels.

This study concluded that HB vaccine stored OCC is as immunoprotective as vaccine stored in cold chain conditions. Also, administering the first dose of HB OCC among children born at home offers an opportunity to substantially improve on-time administration of the first HB vaccine dose.

Study 4: Immunogenicity of a locally produced hepatitis B vaccine with the birth dose stored outside the cold chain in rural Vietnam. Hipgrave DB, Huong VM, Tran TN, et al. American Journal of Tropical Medicine and Hygiene. 2006;74(2):225–260.

This study was performed in three different districts in Vietnam and sponsored by the Australian Agency for International Development. The study compared the immunogenicity of a locally

produced HB vaccine among infants who received three doses stored within the cold chain versus infants who received the first dose stored OCC. The plasma-derived HB vaccine was produced by the National Institute of Hygiene and Epidemiology in Hanoi.⁸

Two vaccination strategies were used. In the first strategy birth doses were administered using vials stored at room temperature (OCC) for up to one month in commune health centers. This was followed by two additional doses stored inside the cold chain (ICC) and given at ages two and three months. In the second strategy, all doses of HB vaccine were stored ICC, and were thus only available on the monthly immunization day.

The study sample size was 1106 infants (9 to 18 months of age). Of those, 748 received the first dose of HB OCC, and 358 received the first dose within the cold chain. A protective level of HB antibodies was present in 80.3% of 1068 infants for whom sufficient serum was available for quantitative testing. There were no significant differences in antibody titers between the two groups.

Study 5: Heat stability of a recombinant DNA hepatitis B vaccine. Van Damme P, Cramm M, Safary A, et al. Vaccine. 1992;10:366–367.

This clinical trial studied the effects of antibody response elicited following administration of an HB vaccine (Engerix-B, SmithKline Beecham Biologicals) that had been stored at elevated temperatures. 138 healthy adults between 18 to 30 years of age took part in the study. They were randomized into three groups to receive the same lot of yeast-derived vaccine stored in three different ways: the first group received vaccine kept at the normal storage temperature (4°C)—control group, the second group received vaccine heated at 45°C for 1 week, and the third group received vaccine heated at 37°C for 1 month. Three 20µg vaccine doses were administered intramuscularly at time points 0, 1, and 6 months.⁹

Blood was drawn from all subjects prior to vaccination for measurement of anti-HBc, anti-HBs, and HBsAg; and at months 1, 2, 6, 7, and 12 for analysis of antibodies. One month after the three vaccine doses, 95-100% of subjects had seroconverted. Six months after the third vaccination, 97-100% of subjects still had measurable titers of antibodies. There was not a statistically significant difference between the groups receiving heated vaccines versus the control group. The heat-treated vaccine groups did not include a greater frequency, severity, or different type of reaction when compared to the control vaccine group.

These results show that the reactogenicity and immunogenicity of the vaccine, including its ability to elicit antibody titers considered protective, are not altered by heating at the stated temperatures and durations.

Study 6: Immunogenicity of a heat-treated recombinant DNA hepatitis B vaccine. Just M, Berger R. Vaccine. 1988;6:399–400.

This study evaluated the effect of heating on the reactogenicity and immunogenicity of a yeast-derived HB vaccine. Recombinant HB vaccine (Engerix-B, GlaxoSmithKline Biologicals) was heated at 37°C for one week. Samples of the same lot were stored at 4°C as a control. 58 healthy young adults without prior serological evidence of HB infection were included in the study. Subjects were randomly assigned to receive either heated vaccine (n=27) or control

vaccine (n=31). They were vaccinated at 0, 1, and 6 months with 20µg of the control or heated vaccine.¹⁰

Heating the HB vaccine to 37°C for one week did not influence its immunogenicity in healthy adults. The overall seroconversion was >98%.

Study 7: Out-of-cold-chain delivery of the HB birth dose in four districts of Vietnam. Huong V, Hipgrave D, Hills S, Nelson C, Sy Hien D, Van Cuong N. PATH (Unpublished data, 2006).

This study was carried out in four districts in northern Vietnam in 2005 and sponsored by PATH. The study evaluated the coverage, safety, immunogenicity, and logistics of an out-of-cold-chain delivery strategy for the HB vaccine birth dose in areas where the cold chain does not function well. There were two groups in the study. The first group consisted of newborns born at the district hospital and vaccinated with the HB vaccine stored in the cold chain. The second group consisted of infants born at commune health centers and at home. These infants were vaccinated with HB stored at room temperature at commune health facilities. For both groups, the subsequent two doses were stored in the cold chain and delivered during regular monthly EPI days at commune health centers. The single-dose HB vaccine for the birth dose was delivered to the health center twice per month and stored at room temperature in a dark box to protect it from sunlight.¹¹

Over 10,000 children in the four districts were vaccinated with the first dose of HB vaccine. Approximately one third of them received the first dose within the cold chain and two thirds OCC. The introduction of the OCC strategy doubled on-time birth dose of HB vaccine according to previous baseline data.

A serologic survey was performed on children from both groups. The group that received the first dose within the cold chain showed a protective antibody level of 86% while the group that received the vaccine OCC showed a protective level of 92%. The reasons for this higher protective level in the OCC group are not clear, but one possibility raised in the study is a reduction in vaccine freezing.

Study 8: Overcoming the need for a cold chain with conjugated meningococcal group C vaccine: A controlled, randomized, double-blind study in toddlers on the safety and immunogenicity of Menjugate, stored at room temperature for 6 months. Schondorf I, Banzhoff A, Nicolay U, Diaz-Mitoma F. Vaccine. 2007; 25:1175–1182.

A controlled, randomized study evaluated the safety and immunogenicity of conjugated meningococcal group C vaccines in toddlers when stored at room temperature for six months. This was a phase IV, stratified-randomized, double blind, multi-center study. A total of 500 toddlers, aged 12-23 months, with no history of prior meningococcal vaccination or disease, and no contact to a person with meningococcal disease within 30 days prior to study entry were stratified according to age (12 to < 16 months n= 242) and (16 to <24 months n=258), and randomly assigned to one of the two study groups: groups W and C.¹²

The vaccine administered to subjects in study group W was stored for six months at room temperature (+25° +/- 2 C). The vaccine administered to subjects in study group C was stored for

six months at 2° to 8°C. Apart from these six months of storage at different temperatures, all vaccines were stored between 2° and 8°C.

All participants had blood drawn for determination of anti-meningococcal C titers prior to immunization on day 1 and 28 days after immunization.

There was no difference in the immune response in toddlers of the two groups. The reactogenicity of the vaccine was similar in both groups and the frequencies of adverse reactions were in the normal range.

Field performance of vaccine vial monitors

The VVM can be seen as a catalyst for much needed changes in the strategies of vaccine distribution via the cold chain. The correct and full use of VVMs can allow immunization programs to benefit from the stability of each vaccine to the greatest possible extent, minimize distribution costs, and increase flexibility in the handling of vaccines in the field thus helping to make operations more effective. The performance of VVMs are well established after years of use, and several laboratory tests have been conducted to help build evidence for the correct correlation between vaccine deterioration and VVM indications.^{13,14,15} This literature review sought published articles that discussed performance of the VVM in the field rather than in laboratory settings. One study was identified that met this criterion.

Study 9: Use of cool water packs to prevent freezing during vaccine transportation at the country level. Kartoglu U, Ganivet S, Guichard S, et al. PDA Journal of Pharmaceutical Science and Technology. 2009;63(1):11–26.

VVMs were used as an indicator of excess heat and freeze exposure in a study that evaluated the use of cool water packs to prevent freezing during transportation at the country level. Part of the study was conducted in a laboratory setting and part in Nepal, Myanmar, Turkey, and Zimbabwe to show temperature variations in a real life situation. The study used different cold boxes, vaccine carriers, data loggers, and all four types of VVMs (VVM2, VVM7, VVM14, and VVM30).¹⁶

In laboratory studies, either dummy vials with VVMs and real vaccines were loaded into various sized cold boxes and vaccine carriers with water packs that had been cooled overnight at 2° to 8°C. The boxes and carriers were then kept at ambient temperatures of 32°C and 43°C.

In country studies cold water packs, prepared as described above, were used to distribute vaccines during routine distribution. In addition, dummy vials labeled with four different types of VVMs were included in some loads.

In both studies, the temperatures inside the carriers were measured, and VVM progression was noted. A method was developed to estimate remaining shelf life of vaccines using VVM readings. Recorded temperature data were used to calculate the amount of the VVM shelf life that had expired.

The study showed that large vaccine carriers at extreme ambient temperatures of 43°C could prevent temperatures rising much above +20°C over 48 hours, and VVM7, VVM14, and VVM30 maintained reasonable remaining shelf lives (all vaccines fall into these categories, except for OPV). These results provide further evidence that VVMs can be effectively used to manage vaccine stock and ensure efficacy of vaccines that are transported outside of a traditional cold chain.

Discussion

Implications of out of the cold chain data for hepatitis B vaccine management

Data presented in this review shows that HB vaccines are thermostable enough to be successfully taken OCC in the final segment of their journey to the child, with no compromise to conferred immunity. In rural areas in particular, where community health workers have difficulty maintaining the recommended temperature ranges for the cold chain, flexible cold chain policies could help increase vaccine coverage. Careful attention should be paid in countries with low-ambient temperatures so that OCC vaccines are not exposed to freezing temperatures.

Vaccine vial monitors

VVMs continue to be recommended by WHO as the gold standard to monitor heat exposure of vaccines and assist with stock management. Because VVMs are specifically designed to monitor and indicate the cumulative heat exposure on an individual vial basis, they are a critical tool to enable safe and effective immunization when vaccines are taken OCC. The study reviewed in this paper confirms the validity of VVM information when vaccines are transported outside of the traditional cold chain.

Other considerations

Despite all the advantages and positive public health implications of implementing an OCC policy, it is important to consider the risks and costs associated with this strategy. There is the risk associated with vaccinating subjects with a heat damaged vaccine resulting in insufficient seroconversion and/or injection-site reactions. There is the risk of confusion in allowing OCC storage for some vaccines but maintaining the cold chain for others.

Furthermore, given that immunization is a preventive measure practiced upon a very young population, immunization practices always bear the burden of ensuring safety as rigorously as possible. The acceptance of immunization in any community is vulnerable and can be tipped by adverse events that occur—even on a very small scale.

To properly manage these risks, it is important that an OCC recommendation provide clear parameters and procedures to follow. Sufficient and high quality training for community health workers and health personnel will also be critical to make clear the principles and practices of OCC and to ensure the correct use of VVMs.

Conclusion

Various studies performed in different field settings have shown that seroconversion rates of children who receive the first dose of HB stored OCC and those who received the first dose ICC had no significant differences. VVMs continue to be an important tool to monitor heat exposure when vaccines are used OCC. It is recommended that WHO consider these data, and identify other data that are needed in order to formulate and publish clear recommendations for countries to implement OCC practices for HB vaccine.

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